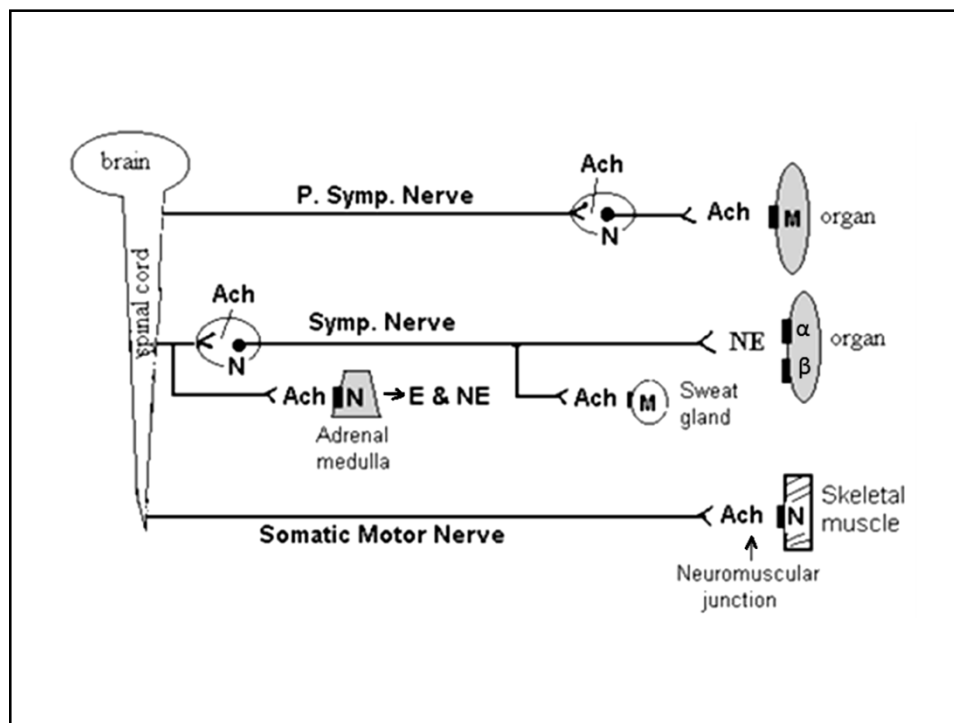


CHOLINERGIC AGONISTS

Parasympathomimetics



THE PARASYMPATHETIC NERVOUS SYSTEM

- The p-sympathetic preganglionic neurons are craniosacral.
- The ganglia lay close to the innervated organs and thus the preganglionic nerves are long and the post ganglionic are short.

Cholinergic fibers: (synthesize and release Ach)

1. Autonomic ganglia (symp and P-symp).
2. Preganglionic fibers to adrenal medulla,
3. Postganglionic fibers of all parasympathetic.
4. Few sympathetic postganglionic fibers (sweat glands and few sympathetic fibers to blood vessels in skeletal muscles).
5. Somatic motor nerve endings (neuromuscular junction, **NMJ**).
6. Certain sites in the CNS.

Neurotransmission at cholinergic neurons

Acetyl Choline is synthesized in the cytoplasm of the terminals of cholinergic nerves.

1-Biosynthesis of Acetyl Choline takes place in two main steps:

- Active transport (through carrier) of choline (4ry ammonium) into the nerve terminal. This is the rate limiting step in Ach synthesis.
- Choline transport can be inhibited by **hemicholinium**.
- Acetylcholine is synthesized from acetyl CoA and choline through the catalytic action of choline acetyltransferase (CAT).



2-Storage of acetyl choline

- Acetylcholine is packed with ATP (cotransmitter) into the synaptic vesicles by an active transport coupled to the efflux of protons.
- The neurotransmitters in vesicles will appear as bead-like structures, known as varicosities.

3-Release of acetylcholine

- When an action potential arrives at a nerve ending, voltage-sensitive Ca^{2+} channels open, causing an increase in the concentration of intracellular Ca^{2+} .
- Elevated Ca^{2+} levels promote the fusion of synaptic vesicles with the cell membrane and release of their contents into the synapse.
- The release is blocked by **botulinum toxins**.

4-Binding to receptors

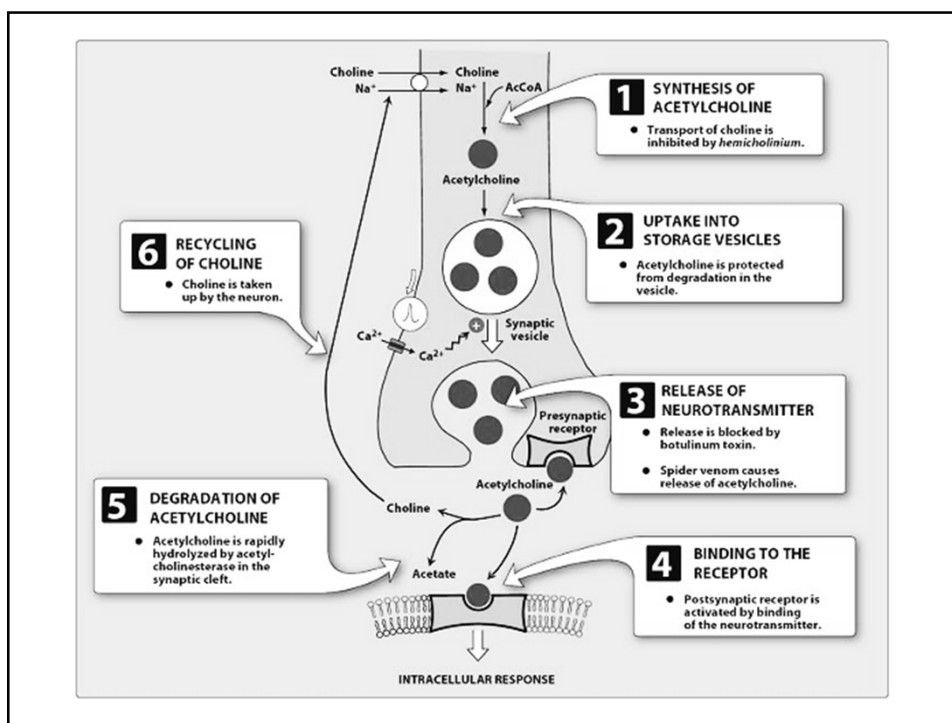
- After release Acetylcholine may bind to and activate a cholinergic receptor (Muscarinic or Nicotinic).

5-Degradation of acetylcholine

- Acetylcholine is broken down by **acetylcholinesterase** enzyme (**AchE**) which splits Ach into choline and acetate.
- Most cholinergic synapses are richly supplied with AchE.
- There are two types of AchE:
 1. True cholinesterase (specific) present in the CNS, RBCs and all cholinergic sites.
 2. Pseudocholinesterase (non specific, butyrylcholinesterase) present in the liver and the plasma.

6-Recycling of choline

- Choline may be recaptured by a sodium-coupled, high-affinity uptake system.



Cholinergic receptors

• Muscarinic receptors

- Located in p-symp effector cells in smooth muscle, cardiac muscle and in presynaptic nerve terminals .
- Selectively stimulated by muscarine and blocked by atropine.
- Mediate the activation of sweat glands by Ach released from sympathetic nerves.
- All M receptors are G-protein coupled receptors.

Locations of Muscarinic receptors

There are 5 genetically distinct receptor subtypes

- **M₁**: in the CNS, peripheral neurons and gastric parietal cells.
- **M₃**: in CNS, peripheral neurons and smooth muscles and in many glands.

Both M₁ and M₃ coupled to G protein (**G_q**) which activates phospholipase C → convert phospholipids to diacylglycerol (DAG) and inositol trisphosphate (IP₃) which cause an increase in intracellular Ca²⁺. DAG also stimulates protein kinase C.

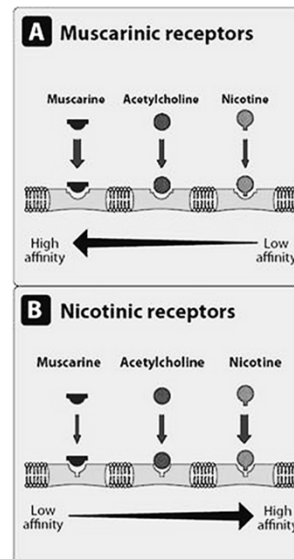
- **M₂**: on the cardiac muscle

M₂ stimulates G protein (**G_i**), that inhibits adenylyl cyclase (↓cAMP) and it opens K⁺ channels → hyperpolarizes the membrane potential and decreases excitability of the cells in SA and AV nodes of the heart (↓HR and ↓force of contraction).

- Some M receptors have specific blockers
 - **Pirenzepine**: blocks M₁ and used for the treatment of peptic ulcer.
 - **Darifenacin**: blocks M₃ and used for the treatment of hyperactive bladder.

• Nicotinic receptors

- They can bind to nicotine and acetylcholine with weak affinity to muscarine.
- Located in autonomic ganglia, CNS, adrenal medulla and NMJ.
- Ganglionic receptors are blocked by Hexamethonium while NMJ receptors are blocked by Tubocurarine
- Nicotine is the classic agonist first stimulates (low conc.) then blocks autonomic ganglia and skeletal muscles end plates (high conc.).
- Activation of nicotinic receptors results in channel opening that allows Na⁺ and K⁺ to diffuse down their concentration gradient.



Cholinergic drugs

Parasympathomimetics

- They can produce some or all the effects that Ach can produce.

Classification

1) Directly acting (agonists at cholinergic receptors)

1. Choline esters: Ach, Methacholine, Carbachol, Bethanecol
2. Cholinomimetic alkaloids: Muscarine, Pilocarpine.

2) Indirectly acting (Anticholinesterases)

1. Reversible : Neostigmine, Physostigmine
2. Irreversible: organic phosphate compounds

Acetylcholine (Ach)

- A quaternary ammonium compound that cannot penetrate membranes.
- Therapeutically of NO importance because it is **NON specific** (M and N) and its rapid inactivation by the cholinesterases.
- The choline moiety contains quaternary ammonium group that gives Ach a permanent positive charge (NOT absorbed orally).

Pharmacological actions of Acetylcholine

Muscarinic effects

I- Cardiovascular system:

- ↓ HR (negative chronotropy) & ↓ cardiac output: Mimic the effect of vagal stimulation. This is mediated by direct stimulation of cardiac M2 receptors in the SA node and AV node. This will lead to increase K⁺ permeability and reduces cAMP levels.
- Vasodilatation & ↓BP (indirect mechanism): Ach activates M3 receptors in endothelial cells lining the smooth muscles of blood vessels → Production of nitric oxide (endothelium-derived relaxing factor) from arginine → stimulate guanylate cyclase → ↑cGMP → ↓Ca²⁺ → Vascular smooth muscle relaxation hyperpolarization.
- Atropine blocks these muscarinic receptors and prevents acetylcholine from producing vasodilation

II-Eye

- Contraction of the circular muscles of iris, causing papillary constriction (miosis).
- Contraction of ciliary muscle leading to accommodation to **near vision**.
- Ach facilitates the outflow of aqueous humor into the canal of schlemm and thus ↓ IOP (Intraocular pressure) in **glaucoma**.

III-GIT

- Ach increases the tone of GIT smooth muscle.
- It enhances peristaltic movement and relaxes GI sphincters.
- It stimulates and enhances the secretion of gastrin, secretin and insulin.

IV-Urinary tract

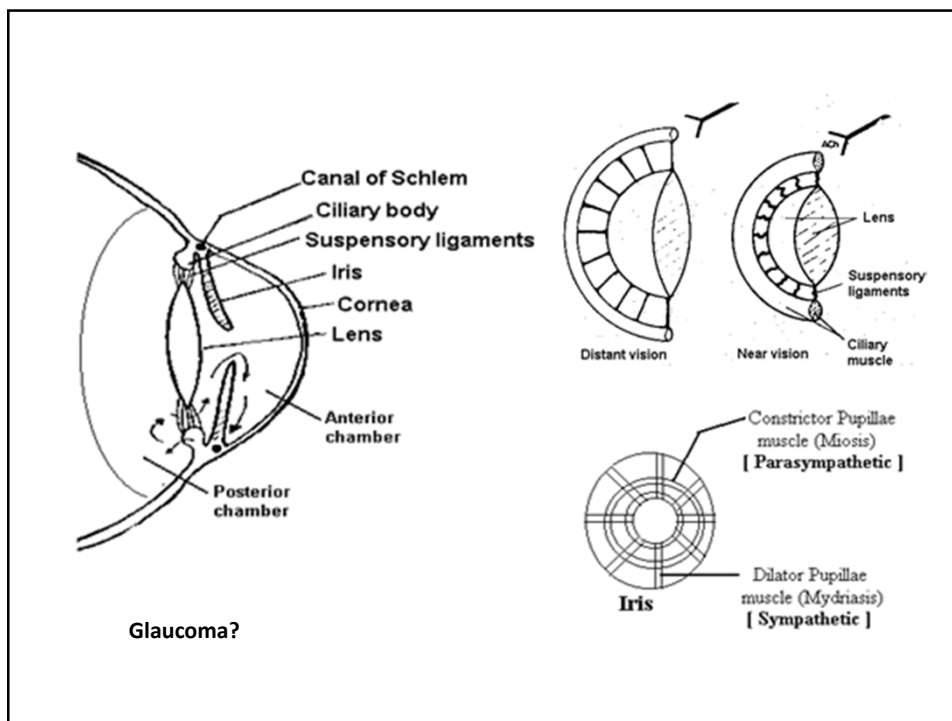
- Contraction of the detrusor muscle and relaxation of the sphincter resulting in evacuation of the bladder.

V- Respiratory system

- Constriction of bronchioles and increased secretion.

VI-Exocrine glands

- Stimulation of salivary, gastric, bronchial, lachrymal and sweat secretion.



Nicotinic Effects

I- On autonomic ganglia:

- Large dose of Ach may increase BP due to the stimulation of adrenal medulla and release of adrenaline and noradrenaline and stimulation of sympathetic ganglia and release of noradrenaline from the post ganglionic sympathetic nerves.

II- On skeletal muscle: Ach leads to twitches and tremors.

Therapeutic uses of Ach

As it is rapidly inactivated by AchE so it is injected into the anterior chamber of the eye to produce miosis during ophthalmic surgery (brief miosis).

Acetylcholine Derivatives

1- Methacholine

- The choline is methylated so it is selective to M receptors
- Resistant to hydrolysis by AchE so it is more potent and has longer duration of action than Ach.
- Used to identify bronchial hyper-reactivity in patients without clinical apparent asthma. This drug is administered by inhalation and patient who develop asthma usually produce an airway contraction.

2-Carbamol (Carbamylcholine)

- The terminal methyl group is replaced by a carbamyl group this makes it completely resistant to degradation by AchE and it is hydrolyzed by other esterases.
- Non selective (M & N).
- Strong effects on CVS (?), GIT (?) due to ganglionic effects (↑ then ↓).
- Release epinephrine from adrenal medulla (N action).
- In the eye, it causes miosis and a spasm of accommodation in which the ciliary muscle of the eye remains in a constant state of contraction.
- Because it is very potent, only used in treatment of glaucoma
- At doses used ophthalmologically, little or no side effects occur due to lack of systemic penetration (quaternary amine).

3-Bethanecol

- The acetate is replaced by carbamate and the choline is methylated.
- It is selective M agonist and resistant to degradation by AchE.
- Weak M actions mainly on smooth muscles bladder and GIT (1 h duration).
- **Used for the treatment of:**
 - Atonic bladder (postpartum or postoperative)
 - Urine retention
 - Neurogenic atony (paralytic ileus).
 - Megacolon (abnormal dilation of the colon accompanied by a paralysis of the peristaltic movements)
- **Adverse effects:**
 - Causes generalized cholinergic stimulation (sweating, salivation, flushing, decreased blood pressure, nausea, abdominal pain, diarrhea, and bronchospasm).

Cholinomimetic alkaloids

Pilocarpine

- Pure **M** agonist (weak) and is not metabolized by AchE.
- It is a tertiary amine that can cross membranes easily and thus rapidly absorbed by the cornea of the eye and can cross BBB.

Pharmacological actions

Eye:

Used orally or locally, it produces miosis, spasm of ciliary muscles leading to accommodation to near objects, decreases IOP.

Smooth muscle:

- Increase GIT tone.
- Bronchoconstriction
- Contraction of the urinary bladder.

Exocrine glands (very potent):

- Stimulates the sweat gland (diaphoretic).
- Stimulation of the salivary glands (sialogogue).
- Lacrimal, gastric and bronchial glands are stimulated.

Therapeutic uses:

- **Glaucoma** (open and closed angle) in **emergency** due to rapid onset (open the canal of Schlemm → ↑ the drainage of aqueous humor → ↓ IOP)
- Alternating with mydriatic to break adhesion between iris and lens.
- Stimulation of saliva in **Xerostomia** (dry mouth) of radiation and **Sjogren's** syndrome (dry mouth and lack of tears).

Adverse Effects:

- It can enter the brain and cause CNS disturbances.
- Poisoning with it show exaggerated p- symapthomimetic effects (Sweating, salivation) similar to toxic mushrooms.
- Headache, loss of eye accommodation, nausea, abdominal cramps, diarrhea, hypotension with reflex tachycardia, bronchoconstriction.
- These actions can be antagonized by atropine.

Contraindications:

- Bronchial asthma.
- Peptic ulcer disease.
- Coronary artery diseases.
- Hypotension or marked bradycardia.
- Parkinsonism.

Indirect-Acting Cholinergic Agonists

Anticholinesterases (Reversible)

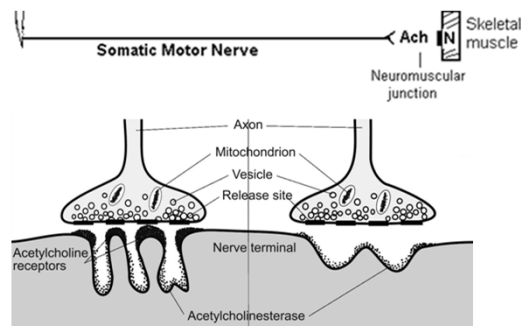
- Inhibitors of AchE indirectly provide a cholinergic action by prolonging the lifetime of Ach at all cholinceptors in the body, including both **M** and **N** receptors of the ANS, NMJ & brain.

A. Edrophonium

- Rapidly absorbed and has a short duration of action of 10 to 20 minutes (rapid renal elimination).
- It is a quaternary amine and is used in the diagnosis of myasthenia gravis (**NOT for treatment, why?**). IV injection of edrophonium leads to a rapid increase in muscle strength.
- Excess drug may provoke a **cholinergic crisis** (Ach over-stimulation at NMJ → muscles stop responding to Ach → leading paralysis, respiratory failure). Atropine is the antidote.
- Uses: diagnosis of myasthenia gravis, determine the over dosage of anticholinesterase (intensify the symptoms) and reverse the action of competitive neuromuscular blockers.

Myasthenia gravis

- MG is an autoimmune disease caused by antibodies to the nicotinic receptor at NMJ. This causes their degradation and, thus, makes fewer receptors available for interaction with the neurotransmitter.
- Symptoms: Muscle weakness, ptosis.
- Treatment:
 - Neostigmine, pyridostigmine and ambenonium
 - Anticholinergic drugs (close M receptors).
 - Immunosuppressive drugs: corticosteroids or azathioprine.



B. Physostigmine

- Physostigmine is found naturally in plants and is a **tertiary amine**.
- Forms a relatively stable intermediate with AchE → reversibly inactivated → potentiation of cholinergic activity throughout the body.
- **Actions:** **M** and **N** receptors of the ANS, **NMJ** and **brain**.
- Its duration of action is about 2 to 4 hours (intermediate-acting agent).
- **Therapeutic uses:**
 - Intestinal and bladder atony
 - Topically in the eye → miosis and spasm of accommodation and ↓IOP so used treat glaucoma (pilocarpine is more effective).
 - Antidote for atropine, phenothiazines, and tricyclic antidepressants.
- **Adverse effects:**
 - CNS → Convulsions (high doses).
 - Bradycardia and a fall in cardiac output.

C. Neostigmine

- A synthetic compound similar to physostigmine.
- **Actions:**
 - Has a **quaternary nitrogen** → it is more polar and does not enter the CNS.
 - Its effect on skeletal muscle is **greater** than that of physostigmine.
 - Has a moderate duration of action, usually 30 minutes to 2 hours.
- **Therapeutic uses:**
 - It is used to stimulate the bladder and GI tract.
 - **Antidote** for tubocurarine and other competitive neuromuscular blockers.
 - Symptomatic treatment of **myasthenia gravis**.
- **Adverse effects**
 - Generalized cholinergic stimulation (salivation, flushing, decreased blood pressure, nausea, abdominal pain, diarrhea, and bronchospasm).
 - **No CNS side effects (why?)** and is not used to overcome toxicity of central-acting antimuscarinic agents such as atropine

C. Pyridostigmine and ambenonium

- Used in the **chronic** management of myasthenia gravis.
- Their durations of action are intermediate (3 to 6 hours and 4 to 8 hours, respectively), but longer than that of neostigmine.
- Adverse effects: similar to neostigmine.

F. Tacrine, donepezil, rivastigmine, and galantamine

- Used for patients with **Alzheimer's** disease (have a deficiency of cholinergic neurons in the CNS).
- Tacrine was the 1st one but it is replaced by the others because of its hepatotoxicity.
- They **delay** the progression of the disease, none can stop it.
- Adverse effect: GIT distress.

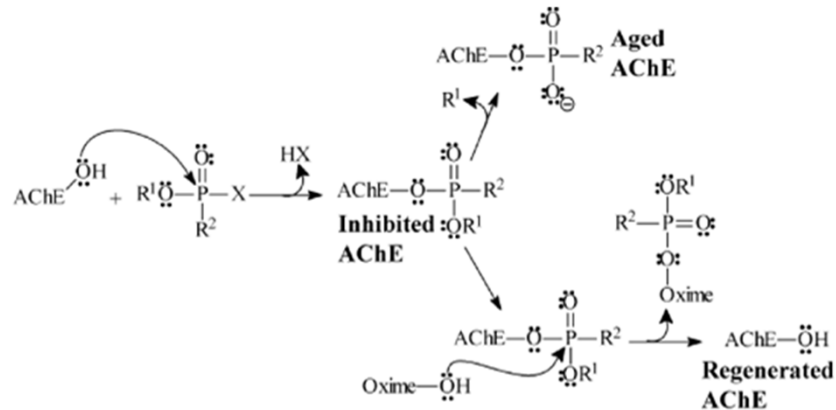
Indirect-Acting Cholinergic Agonists

Anticholinesterases (Irreversible)

- Some **organophosphate** compounds bind covalently to AchE → long-lasting increase in Ach at all sites where it is released.
- Extremely toxic as nerve gas or parathion (insecticides).

Echothiophate

- **Mechanism of action:**
 - It covalently binds AchE → the enzyme is permanently inactivated
 - Restoration of AchE activity requires the synthesis of new enzyme.
 - Following covalent modification of AchE, the phosphorylated enzyme releases one of its ethyl groups. The loss of an alkyl group, which is called **aging**, makes it impossible for chemical reactivators (**pralidoxime**) to break the bond between the drug and enzyme.
- **Actions:**
 - Generalized cholinergic stimulation, paralysis of motor function (causing breathing difficulties), and convulsions and intense miosis (**Atrpaine** is the anti-dote).
- **Therapeutic uses:**
 - Used directly in the eye for the chronic treatment of **open-angle glaucoma** (one week duration after a single administration).
 - Limited use (may cause cataract).



Pralidoxime Mechanism of Action

Toxicology of AchE inhibitors

AChE inhibitors usually cause toxicity because they are insecticides or used for suicide → Toxicity signs due to N and M actions.

Reactivation of AchE:

- **Pralidoxime (PAM)** can reactivate inhibited AChE (before aging) but it is unable to penetrate into the CNS.
- The presence of a charged group allows it to approach an anionic site on the enzyme, where it displaces the phosphate group of the organophosphate and regenerates the enzyme.
- New nerve agents produce aging of the enzyme complex within seconds, so pralidoxime is less effective.
- Pralidoxime is a weak AChE inhibitor and, at higher doses, may cause side effects similar to other AChE inhibitors.

Other agents:

- Atropine: prevent M actions (Bronchoconstriction, bradycardia and increased secretions).
- Diazepam: reduce convulsions.
- Oxygen and artificial respiration.

